Tab 26

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Letter to the Editor:

Since the publication of our paper "An acute clinical trial evaluating the cardiovascular effects of an herbal ephedra-caffeine weight loss product in healthy overweight adults", *International Journal of Obesity* (2002),26,1363-1366. we have reanalyzed the adverse events data.

While no statistically significant differences between treatment and placebo were demonstrated within specific event types or organ system categories, a significantly ($p=0.004$) larger proportion of Xenadrine RFA-1™ subjects than placebo controls experienced adverse events (including treatment-related and non-treatment-related events). The most frequent treatment and non treatment related events were dry mouth, increased activity, and upper respiratory tract infection, each of which occurred in 20% of Xenadrine RFA-1™ subjects but in no Placebo controls, and sleep disorders, which occurred in 30% of Xenadrine RFA-1™ subjects but in 10% of Placebo controls. The small sample size could explain the lack of statistical significance. Since there were no serious adverse events and we observed no differences between placebo and treatment with regard to cardiovascular measurements (echocardiograms, electrocardiograms and blood pressure), our conclusion regarding the safety of the treatment in healthy subjects treated for two weeks remains unchanged.

Sincerely,

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Adverse Event Report for Study:

XEN-501

"A Double Blind Placebo Controlled Clinical Evaluation of the Sympathomimetic Effects of Xenadrine RFA-1™ in Healthy Overweight Volunteers"

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1. Introduction

This document contains an analysis of the adverse events (AEs) occurring in the study, *[Need Title]* (Cytodyne Technology Study XEN-501).

Detailed (event-level) tables include a listing of the raw data on each event, and a listing of the MedDRA coding (Preferred Term Code and Description, and Organ System Code and Description).

Summary tables include breakdowns of event counts and subject counts by Preferred Term and by Organ System, for each treatment group (Xenadrine and Placebo), for all events and for drug-related events. The two treatment groups are compared statistically to assess whether the proportion of subjects with AEs is different in the two groups.

2. Listing of All Adverse Events

The following table shows a listing of adverse events (if any) for all subjects enrolled in the study, as reported by Miami Research, Inc.

Table 1. Listing of Adverse Events.

Group	ID	Subj	Status	Dates (all in 1991)	Adverse Event	Severity	SAE?	Rel to Drug
XEN	1	LZC	Finished	Jul 22 - Jul 27	URI	Mild	No	NoRel
XEN	1	LZC	Finished	Jul 24 - Aug 1	sleep disturbance	Mild Mod	No	Prob
XEN	1	LZC	Finished	Jul 26 - Jul 31	dry mouth	Mild	No	Poss
XEN	3	LAE	Finished		no AE's			
XEN	4	MIQ	Drop AE	Jul 22 - Jul 22	chest pain	Mild	No	Prob
XEN	4	MIQ	Drop AE	Jul 22 - Jul 22	shortness of breath	Mild	No	Prob
XEN	5	JC	Finished	Aug 30 - Aug 9	tachycardia	Mod	No	Poss
XEN	7	RF	Finished		no AE's			
XEN	8	SL	Finished	Jul 1 - Jul 5	irritability	Mod	No	Prob
XEN	8	SL	Finished	Jul 1 - Jul 2	sleep disturbance	Mod	No	Prob
XEN	9	PAB	Finished	Jun 21 - Jun 27	dry mouth	Mild	No	Prob
XEN	9	PAB	Finished	Jun 23 - Jun 29	sleep disturbance	Mild	No	Prob
XEN	10	EAK	Finished	Jul 12 - Jul 13	jitteriness	Mild	No	Prob
XEN	10	EAK	Finished	Jul 13 - Jul 26	dry mouth	Mild	No	Prob
XEN	10	EAK	Finished	Jul 14 - Jul 26	hyperactivity	Mild	No	Prob

Group	ID	Subj	Status	Dates (all in 1991)	Adverse Event	Severity	SAE?	Rel to Drug
XEN	10	EAK	Finished	Jul 14 - Jul 27	sleep disturbance	Mild	No	Prob
XEN	10	EAK	Finished	Jul 17 - Jul 19	URI	Mild	No	NoRel
XEN	11	PB	Finished	Jun 22 - Jun 29	increased thirst	Mild	No	Prob
XEN	11	PB	Finished	Jun 22 - Jun 25	sleep disturbance	Mod	No	Prob
XEN	12	JOP	Finished	Jun 27 - Jul 5	scratchy throat	Mild	No	PrNot
XEN	13	ELN	Finished	Jul 18 - Jul 19	diarrhea	Sev	No	PrNot
XEN	13	ELN	Finished	Jul 19 - Jul 20	nausea	Sev	No	PrNot
XEN	13	ELN	Finished	Jul 19 - Jul 20	vomitting	Sev	No	PrNot
XEN	13	ELN	Finished	Jul 23 - Jul 24	hyperactivity	Mild	No	Prob
XEN	13	ELN	Finished	Jul 23 - Jul 24	increased sweating	Mild	No	Poss
XEN	14	EJH	Finished	Jun 8 - Jun 21	depressed	Mild	No	NoRel
XEN	14	EJH	Finished	Jun 8 - Jun 23	dry mouth	Mild	No	Prob
XEN	14	EJH	Finished	Jun 8 - Jun 21	lack of energy	Mild	No	NoRel
XEN	14	EJH	Finished	Jun 8 - Jun 20	sleep disturbance	Mild	No	Prob
XEN	15	TWB	Finished		no AE's			
XEN	16	BIA	Finished	Jul 12 - Jul 14	hyperactivity	Mod	No	Prob
XEN	17	KGR	Finished	Jun 21 - Jun 23	allergic rxn mango	Mod	No	NoRel
XEN	17	KGR	Finished	Jun 27 - Jun 29	headaches	Mod	No	PrNot
XEN	18	LP	Finished		no AE's			
XEN	19	RA	Finished	Jul 5 - Jul 5	upset stomach	Mod	No	Prob
XEN	19	RA	Finished	Jul 18 - Jul 19	URI	Mod	No	PrNot NoRel
XEN	20	JOL	Finished	Jul 13 - Jul 20	increased BM's	Mild	No	PrNot
XEN	34	MJV	Finished	Jun 14 - Jun 17	headache	Mild	No	Poss
XEN	34	MJV	Finished	Jun 15 - Jun 30	increased thirst	Mild	No	Poss
XEN	50	JMF	Finished	Jun 14 - Jun 15	hyperactivity	Mild	No	Prob
XEN	50	JMF	Finished	Jun 18 - Jun 20	URI	Mild	No	NoRel
Plac	21	ATM	Finished		no AE's			
Plac	22	JAA	Finished		no AE's			
Plac	23	MG	Finished		no AE's			
Plac	24	GP	Finished		no AE's			
Plac	25	RBA	Lost FU		no AE's			
Plac	26	KEC	Finished		no AE's			
Plac	27	ARF	Finished		no AE's			
Plac	28	GA	Finished	Jul 20 - Jul 25	sleep disturbance	Mod	No	Prob

Group	ID	Subj	Status	Dates (all in 1991)	Adverse Event	Severity	SAE?	Rel to Drug
Plac	28	GA	Finished	Jul 30 - Jul 31	dry cough	Mod	No	PrNot
Plac	29	AT	Finished	Jun 27 - Jun 27	headache	Mild	No	NoRel
Plac	30	SC	Scr Fail		no AE's			

Codes used in Table 1:

Group: Plac=Placebo; XEN=Xenadrine

Status: Scr Fail=Screening failure; Lost FU=Lost to follow-up; Drop AE=Dropped out of study because of adverse events; Finished=Completed the study

Severity: Mild=Mild; Mod=Moderate; Sev=Severe

Relation to Drug: NoRel=No relation; PrNot=Probably not related; Poss=Possibly related; Prob=Probably related

3. MedDRA Coding

MedDRA is the coding system preferred by the FDA for reporting and tabulating adverse events. There are over 50,000 specifically-worded AEs in the current MedDRA dictionary, many of which are redundant, differing only in minor wording or spelling details, such as "Aplastic anemia", Aplastic anaemia", Anemia aplastic", and "Anaemia aplastic", each having its own distinct 8-digit "low-level code". These redundancies are resolved by rolling up all equivalent terms into a single "preferred term" (in this case, "Aplastic anaemia" with a single code: 10002967). Each preferred term falls within one of 26 general "organ systems", which form the highest-level grouping within the MedDRA system.

All AE descriptions were matched to the closest MedDRA (version 5) entry, using custom-written text-matching software. The corresponding Preferred Term and Organ System was recorded into the XEN-501 database and used for subsequent tabulations.

Table 2 shows the MedDRA Preferred Terms and Organ Systems corresponding to all adverse events recorded in the study.

Table 2. MedDRA Preferred Terms and Organ Systems for all Adverse Events.

Group	ID	Adverse Event as Reported	MedDRA PT Code	MedDRA Preferred Term	MedDRA Organ System
XEN	1	dry mouth	10013781	Dry mouth	Gastrointestinal
XEN	1	URI	10046307	Upper respiratory tract infection NOS	Infections
XEN	1	sleep disturbance	10040989	Sleep disorder NOS	Psychiatric
XEN	4	chest pain	10008479	Chest pain	General
XEN	4	shortness of breath	10013972	Dyspnoea NOS	Resp, Thor, Mediast

Group	ID	Adverse Event as Reported	MedDRA PT Code	MedDRA Preferred Term	MedDRA Organ System
XEN	5	tachycardia	10043078	Tachycardia NOS	Cardiac
XEN	8	irritability	10022998	Irritability	Psychiatric
XEN	8	sleep disturbance	10040989	Sleep disorder NOS	Psychiatric
XEN	9	dry mouth	10013781	Dry mouth	Gastrointestinal
XEN	9	sleep disturbance	10040989	Sleep disorder NOS	Psychiatric
XEN	10	dry mouth	10013781	Dry mouth	Gastrointestinal
XEN	10	jitteriness	10016338	Feeling jittery	General
XEN	10	URI	10046307	Upper respiratory tract infection NOS	Infections
XEN	10	hyperactivity	10021650	Increased activity	Nervous System
XEN	10	sleep disturbance	10040989	Sleep disorder NOS	Psychiatric
XEN	11	increased thirst	10043458	Thirst	General
XEN	11	sleep disturbance	10040989	Sleep disorder NOS	Psychiatric
XEN	12	scratchy throat	10043521	Throat irritation	Resp, Thor, Mediast
XEN	13	diarrhea	10012745	Diarrhoea NOS	Gastrointestinal
XEN	13	nausea	10028813	Nausea	Gastrointestinal
XEN	13	vomitting	10047706	Vomiting NOS	Gastrointestinal
XEN	13	hyperactivity	10021650	Increased activity	Nervous System
XEN	13	increased sweating	10042667	Sweating increased	Skin & Subcut
XEN	14	dry mouth	10013781	Dry mouth	Gastrointestinal
XEN	14	lack of energy	10016256	Fatigue	General
XEN	14	depressed	10012378	Depression	Psychiatric
XEN	14	sleep disturbance	10040989	Sleep disorder NOS	Psychiatric
XEN	16	hyperactivity	10021650	Increased activity	Nervous System
XEN	17	allergic rxn mango	10020755	Hypersensitivity NOS	Immune System
XEN	17	headaches	10019218	Headache NOS	Nervous System
XEN	19	upset stomach	10013946	Dyspepsia	Gastrointestinal
XEN	19	URI	10046307	Upper respiratory tract infection NOS	Infections
XEN	20	increased BM's	10017367	Frequent bowel movements	Gastrointestinal
XEN	34	increased thirst	10043458	Thirst	General
XEN	34	headache	10019218	Headache NOS	Nervous System
XEN	50	URI	10046307	Upper respiratory tract infection NOS	Infections
XEN	50	hyperactivity	10021650	Increased activity	Nervous System

Group	ID	Adverse Event as Reported	MedDRA PT Code	MedDRA Preferred Term	MedDRA Organ System
Plac	28	sleep disturbance	10040989	Sleep disorder NOS	Psychiatric
Plac	28	dry cough	10011224	Cough	Resp, Thor, Mediast
Plac	29	headache	10019218	Headache NOS	Nervous System

3. Comparison of Adverse Events Between Treatment Groups

Tables 3 through 6 show cross-tabulations of adverse events by treatment groups.

The rows of the table correspond summaries by specific MedDRA Preferred Terms (Tables 3 and 5) or MedDRA Organ Systems Tables 4 and 6).

There are three pairs of columns showing the number of occurrences of each category of event, and the number of subjects having at least one occurrence of an event in that category, tabulated for each treatment group, and for the two groups combined.

The patient counts in the following tables should be considered in relation to the total number of enrolled subjects (in the "Safety Population"): 20 in the Xenadrine group, and 10 in the Placebo group.

The last column contains a p-value that indicates whether the proportion of subjects having the event differs between treatment groups ($p<0.05$ indicates a significant between-group difference). This value is computed using the Fisher Exact test. In light of the large number of significance tests performed, the p values should be considered only as descriptive, and significant p values should be interpreted with caution.

Tables 3 and 4 pertain to **all AEs**, whether or not they were considered to be drug-related. Tables 5 and 6 pertain only to **drug-related AEs** (those judged to be definitely, probably, or possibly drug-related, excluding those judged to be not or probably not drug-related).

[It is possible to produce tabulations that break events down by other characteristics, such as severity, duration, dose level, etc. These are most often done in larger studies, involving hundreds of subjects and thousands of AEs, in which it is difficult, if not impossible, to detect patterns in extremely lengthy listings of individual events. But in smaller studies such as this, such higher-level subtotaling would produce large tables with mostly empty cells, and would not be any more informative that a simple perusal of the detailed listing of AEs. For this reason, the cross-tabulations were limited to those presented below.]

3.1 All Adverse Events, by MedDRA Preferred Term, by Treatment Group

Table 3 shows a cross-tabulation of all AEs, regardless of whether or not they were drug-related), summarized by MedDRA Preferred Term, and compared between the Xenadrine and Placebo groups.

Table 3. All Adverse Events, by MedDRA Preferred Term, by Treatment Group.

Event Type	Xenadrine Group		Placebo Group		Both Groups		p value
	Subjects	Events	Subjects	Events	Subjects	Events	
Hypersensitivity	1	1	0	0	1	1	1.000
Chest Pain	1	1	0	0	1	1	1.000
Depression	1	1	0	0	1	1	1.000
Diarrhea	1	1	0	0	1	1	1.000
Cough	0	0	1	1	1	1	0.333
Dry Mouth	4	4	0	0	4	4	0.272
Headache	2	2	1	1	3	3	1.000
Increased Activity	4	4	0	0	4	4	0.272
Frequent Bowel Mvmts	1	1	0	0	1	1	1.000
Sweating	1	1	0	0	1	1	1.000
Thirst	2	2	0	0	2	2	0.540
Irritability	1	1	0	0	1	1	1.000
Jitteriness	1	1	0	0	1	1	1.000
Fatigue	1	1	0	0	1	1	1.000
Nausea	1	1	0	0	1	1	1.000
Throat Irritation	1	1	0	0	1	1	1.000
Dyspnea	1	1	0	0	1	1	1.000
Sleep Disorders	6	6	1	1	7	7	0.372
Tachycardia	1	1	0	0	1	1	1.000
Dyspepsia	1	1	0	0	1	1	1.000
Upper Resp Trk Infect	4	4	0	0	4	4	0.272
Vomiting	1	1	0	0	1	1	1.000
Any Event	**16**	**37**	**2**	**3**	**18**	**40**	**0.004**

Overall, there is a very significantly ($p=0.004$) larger proportion of patients with AEs in the Xenadrine group (16/20, or 80%) than in the Placebo group (2/10, or 20%).

No significant between-group difference in the prevalence of AEs can be demonstrated within any specific type of event (at the MedDRA Preferred Term level), which may be due to the small number of subjects studied.

The most noticeable differences (although not statistically significant) are with respect to **dry mouth, increased activity**, and **upper respiratory tract infection**, each of which occurred in 20% of Xenadrine subjects but in no Placebo controls, and **sleep disorders**, which occurred in 30% of Xenadrine subjects but in only 10% of Placebo controls.

3.2 All Adverse Events, by MedDRA Organ System, by Treatment Group

Table 4 shows a cross-tabulation of all AEs, regardless of whether or not they were drug-related), summarized by MedDRA Organ System, and compared between the Xenadrine and Placebo groups.

Table 4. All Adverse Events, by MedDRA Organ System, by Treatment Group.

Event Type	Xenadrine Group		Placebo Group		Both Groups		P value
	Subjects	Events	Subjects	Events	Subjects	Events	
Cardiac	1	1	0	0	1	1	1.000
Gastrointestinal	7	9	0	0	7	9	0.064
General	5	5	0	0	5	5	0.140
Immune System	1	1	0	0	1	1	1.000
Infections	4	4	0	0	4	4	0.272
Nervous System	6	6	1	1	7	7	0.372
Psychiatric	6	8	1	1	7	9	0.372
Respiratory	2	2	1	1	3	3	1.000
Skin	1	1	0	0	1	1	1.000
Any System	**16**	**37**	**2**	**3**	**18**	**40**	**0.004**

Overall, there is a very significantly (p=0.004) larger proportion of patients with AEs in the Xenadrine group (16/20, or 80%) than in the Placebo group (2/10, or 20%).

No significant between-group difference in the prevalence of AEs can be demonstrated within any specific type of event (at the MedDRA Preferred Term level), which may be due to the small number of subjects studied.

The most noticeable differences are with respect to the **gastrointestinal, general, infections, nervous system**, and **psychiatric** organ system categories for which there appeared to be a substantially larger (but not statistically significantly larger) proportion of Xenadrine subjects experiencing the AEs than Placebo controls.

3.3 Drug-related AEs, by MedDRA Preferred Term, by Treatment Group

The dichotomization of the five-level "related to drug" scale is somewhat arbitrary, depending on how stringently one wishes to interpret the three intermediate categories. I have chosen to define "Drug-Related" as consisting of "Definitely Related" "Probably

Related", and "Possibly Related", and excluding, "Probably Not Related" and "Definitely Not Related". Other definitions are possible.

Table 5 shows a cross-tabulation of drug-related AEs, summarized by MedDRA Preferred Term, and compared between the Xenadrine and Placebo groups.

Table 5. Drug-related AEs, by MedDRA Preferred Term, by Treatment Group.

Event Type	Xenadrine Group		Placebo Group		Both Groups		P value
	Subjects	Events	Subjects	Events	Subjects	Events	
Hypersensitivity	0	0	0	0	0	0	1.000
Chest Pain	1	1	0	0	1	1	1.000
Depression	0	0	0	0	0	0	1.000
Diarrhea	0	0	0	0	0	0	1.000
Cough	0	0	0	0	0	0	1.000
Dry Mouth	4	4	0	0	4	4	0.272
Headache	1	1	0	0	1	1	1.000
Increased Activity	4	4	0	0	4	4	0.272
Frequent Bowel Mvmts	0	0	0	0	0	0	1.000
Sweating	1	1	0	0	1	1	1.000
Thirst	2	2	0	0	2	2	0.540
Irritability	1	1	0	0	1	1	1.000
Jitteriness	1	1	0	0	1	1	1.000
Fatigue	0	0	0	0	0	0	1.000
Nausea	0	0	0	0	0	0	1.000
Throat Irritation	0	0	0	0	0	0	1.000
Dyspnea	1	1	0	0	1	1	1.000
Sleep Disorders	6	6	1	1	7	7	0.372
Tachycardia	1	1	0	0	1	1	1.000
Dyspepsia	1	1	0	0	1	1	1.000
Upper Resp Trk Infect	0	0	0	0	0	0	1.000
Vomiting	0	0	0	0	0	0	1.000
Any Event	**13**	**24**	**1**	**1**	**15**	**25**	**0.007**

Overall, there is a very significantly (p=0.007) larger proportion of patients with drug-related AEs in the Xenadrine group (13/20, or 65%) than in the Placebo group (1/10, or 10%).

No significant between-group difference in the prevalence of drug-related AEs be demonstrated within any specific type of event (at the MedDRA Preferred Term level), which may be due to the small number of subjects studied.

The most noticeable differences (although not statistically significant) are with respect to drug-related **dry mouth** and **increased activity**, each of which occurred in 20% of Xenadrine subjects but in no Placebo controls, and drug-related **sleep disorders**, which occurred in 30% of Xenadrine subjects but in only 10% of Placebo controls.

3.4 Drug-related AEs, by MedDRA Organ System, by Treatment Group

Table 6 shows a cross-tabulation of drug-related AEs, summarized by MedDRA Organ System, and compared between the Xenadrine and Placebo groups.

Table 6. Drug-related AEs, by MedDRA Organ System, by Treatment Group.

Event Type	Xenadrine Group		Placebo Group		Both Groups		P value
	Subjects	Events	Subjects	Events	Subjects	Events	
Cardiac	1	1	0	0	1	1	1.000
Gastrointestinal	5	5	0	0	5	5	0.140
General	4	4	0	0	4	4	0.272
Immune System	0	0	0	0	0	0	1.000
Infections	0	0	0	0	0	0	1.000
Nervous System	5	5	0	0	5	5	0.140
Psychiatric	6	7	1	1	7	8	0.372
Respiratory	1	1	0	0	1	1	1.000
Skin	1	1	0	0	1	1	1.000
Any System	**13**	**24**	**1**	**1**	**15**	**25**	**0.007**

Overall, there is a very significantly ($p=0.007$) larger proportion of patients with drug-related AEs in the Xenadrine group (13/20, or 65%) than in the Placebo group (1/10, or 10%).

No significant between-group difference in the prevalence of drug-related AEs can be demonstrated within any specific type of event (at the MedDRA Organ System level), which may be due to the small number of subjects studied.

The most noticeable differences are with respect to the **gastrointestinal**, **general**, **nervous system**, and **psychiatric** organ system categories for which there appeared to be a substantially larger (but not statistically significantly larger) proportion of Xenadrine subjects experiencing drug-related AEs than Placebo controls.

4. Serious Adverse Events.

No Serious Adverse Events were reported in this study.

5. Conclusions

A significantly (p=0.004) larger proportion of Xenadrine subjects than placebo controls experienced adverse events (including drug-related and non-drug-related events). No statistically significant differences could demonstrated within specific event types or organ system categories, perhaps due to the small number of subjects studied, but there were noticeable increases with respect to **dry mouth**, **increased activity**, and **upper respiratory tract infection**. each of which occurred in 20% of Xenadrine subjects but in no Placebo controls. and **sleep disorders**, which occurred in 30% of Xenadrine subjects but in only 10% of Placebo controls. A larger proportion of Xenadrine subjects experienced AEs than Placebo controls in the **gastrointestinal**, **general**, **infections**, **nervous system**. and **psychiatric** organ system categories.

A significantly (p=0.007) larger proportion of Xenadrine subjects than placebo controls experienced **drug-related** adverse events (including drug-related and non-drug-related events). No statistically significant differences could demonstrated within specific event types or organ system categories, perhaps due to the small number of subjects studied, but there were noticeable increases with respect to drug-related **dry mouth** and **increased activity**. each of which occurred in 20% of Xenadrine subjects but in no Placebo controls. anddrug-related **sleep disorders**. which occurred in 30% of Xenadrine subjects but in only 10% of Placebo controls. A larger proportion of Xenadrine subjects experienced AEs than Placebo controls in the **gastrointestinal**, **general**, **nervous system**, and **psychiatric** organ system categories.

No serious adverse events were recorded during this study.